

Primate microbiomes over time: Longitudinal answers to standing questions in microbiome research

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Abstract

To date, most insights into the processes shaping vertebrate gut microbiomes have emerged from studies with cross-sectional designs. While this approach has been valuable, emerging time series analyses on vertebrate gut microbiomes show that gut microbial composition can change rapidly from 1 day to the next, with consequences for host physical functioning, health, and fitness. Hence, the next frontier of microbiome research will require longitudinal perspectives. Here we argue that primatologists, with their traditional focus on tracking the lives of individual animals and familiarity with longitudinal fecal sampling, are well positioned to conduct research at the forefront of gut microbiome dynamics. We begin by reviewing some of the most important ecological processes governing microbiome change over time, and briefly summarizing statistical challenges and approaches to microbiome time series analysis. We then introduce five questions of general interest to microbiome science where we think field-based primate studies are especially well positioned to fill major gaps: (a) Do early life events shape gut microbiome composition in adulthood? (b) Do shifting social landscapes cause gut microbial change? (c) Are gut microbiome phenotypes heritable across variable environments? (d) Does the gut microbiome show signs of host aging? And (e) do gut microbiome composition and dynamics predict host health and fitness? For all of these questions, we highlight areas where primatologists are uniquely positioned to make substantial contributions. We review preliminary evidence, discuss possible study designs, and suggest future directions.

Research Highlights

- To date nearly all insights into the processes shaping vertebrate gut microbiomes have emerged from studies that have cross-sectional designs, but emerging time series analyses show that gut microbiomes can change rapidly from 1 day to the next.
- Field-based primate studies, owing to their focus on the lives of individual animals, and the relative ease of collecting longitudinal fecal samples from known animals, are better positioned to collect these data than studies of humans or other species.
- We propose five questions of general interest to microbiome science where field-based primate studies are especially well positioned to fill major gaps. We review preliminary evidence, discuss possible study designs, and suggest future directions.

KEYWORDS

community dynamics, fitness, health, longitudinal, microbial ecology, time series

1 | INTRODUCTION

Microbiomes are multilayered, interconnected networks of microbes and their genes, which interact in time and space to produce a well-functioning host (Figure 1). Over the last decade, with the advent of culture-free techniques, researchers have uncovered astonishing diversity in animal microbiomes, especially in the mammalian gut (Bálint et al., 2016). The gut microbiome's composition and diversity is shaped by many factors, including the host's evolutionary history, lifestyle, diet, and social interactions (e.g., David et al., 2013; Moeller, Caro-Quintero, et al., 2016; Moeller, Foerster, et al.,

2016). Some of these compositional differences may have functional consequences for the services gut microbiomes provide to their hosts, including the host's ability to digest complex carbohydrates, detoxify plant secondary compounds, and resist infectious diseases (Kohl & Dearing, 2016; McKenney, Koelle, Dunn, & Yoder, 2018).

To date, many of these insights have emerged from cross-sectional studies, which provide only a snapshot perspective on the gut microbiome at a single time point in a host's life. However, a handful of influential *time series analyses* (see Box 1 for our glossary) on vertebrate gut microbiomes suggest considerable dynamism: Microbial presence and abundance can change considerably from 1

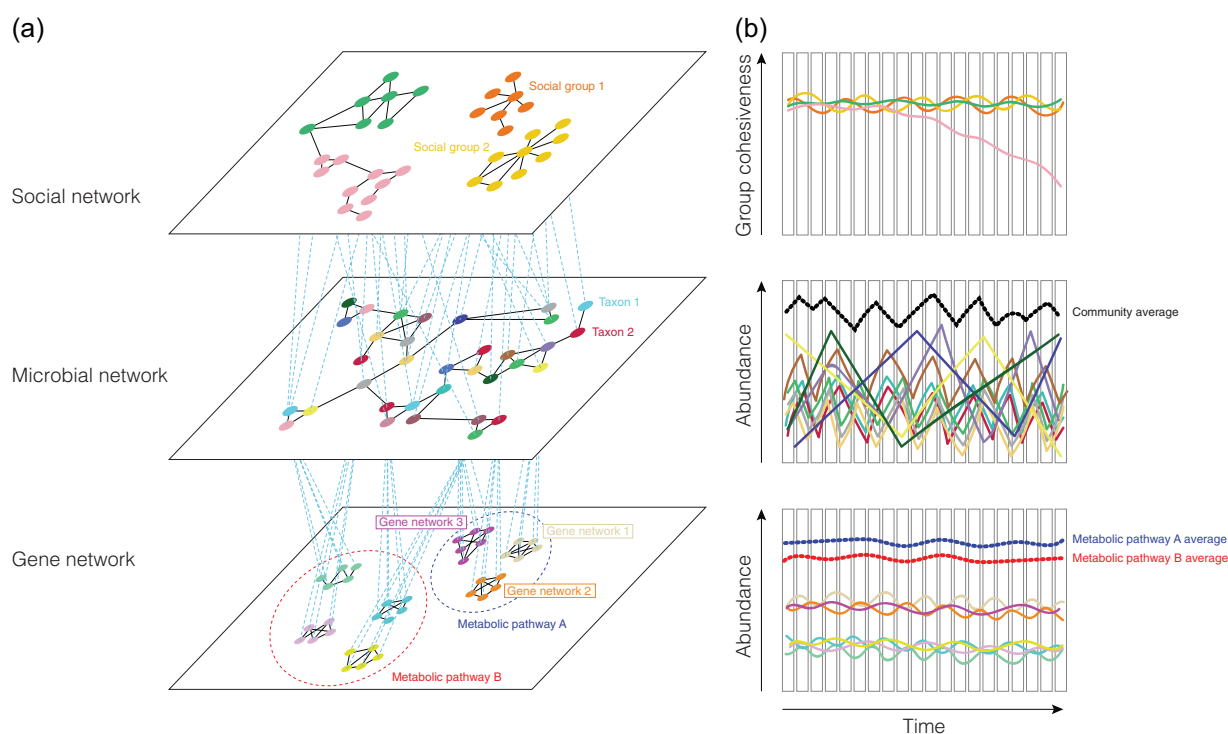


FIGURE 1 A multilayer representation of hosts and their collective gut microbial communities. (a) In this conceptual figure, the microbiome at time t is represented as a multilayer network where layers are squares, solid black lines are intra-layer edges, and dashed blue lines are interlayer edges. The first layer is a social network: Circles represent individual hosts and edges represent social interactions between hosts living in the same and different social groups, depicted by different colors. The second layer is a gut microbial network: Circles represent individual microbial taxa, depicted by different colors, and edges represent positive and negative relationships between taxa. The third layer is a gene network: Circles represent gut microbial genes, and edges represent genes that are found in the same gene network, represented by different colors. Different metabolic pathways can be responsible for the same function; the dashed red and blue circles depict functionally redundant metabolic pathways (e.g., the degradation of cellulose or pectin). Multiple metabolic pathways can be present in the same microbe, and multiple microbes can have the same metabolic pathways, but for illustrative purposes, this is not depicted. The interlayer edges represent different types of associations; edges connect hosts and microbes when that microbe is found in a given host; edges connect microbes and genes when that metabolic pathway is present in a given microbe. (b) Longitudinal time series allow for analyzing how different properties of each layer change over time. Each bar represents a given layer at time $t \in \{1, 2, \dots, T\}$. For instance, in the top plot, cohesiveness among social groups changes over time due to the fission and fusion of social groups. In the second plot, gut microbial taxa change in abundance over time due to similar or different responses to biotic and abiotic factors. Each colored line corresponds to a microbial taxa and the thick black dashed line represents the aggregated fluctuations at the whole microbiome community level. In the last plot, individual metabolic pathways fluctuate over time (depicted by thin colored lines), but due to functional redundancy, the host's functional capacity is stable over time (red and blue thick dashed lines). See Piloşof et al. (2017) for a review of multilayer networks in ecology

BOX 1 Glossary

Alternative stable states. Different possible stable states of composition or function that a community can move to, either following a perturbation or because of different initial conditions (Beisner, Haydon, & Cuddington, 2003).

Complex adaptive systems. A system in which many independent agents interact, leading to emergent outcomes that are often difficult or impossible to predict simply by observing individual interactions (Lansing, 2003).

Dispersal. The movement of species across space (Vellend, 2016).

Drift. Random changes in population sizes via stochastic birth and death events (Vellend, 2016).

Dynamical system. The mathematical notion of a dynamical system consists of two parts: the *phase space* and the *dynamics*. The phase space of a dynamical system is the collection of all possible states of the system in question. Each state represents a complete snapshot of the system at some moment in time. The dynamics are governed by rules (state variables) that transform the state of the system at time t into a new state at time $t + 1$. For instance, a principal coordinates analysis plot depicting microbiome similarity can be viewed as the phase space (Didier et al., 2018).

Feedback loops. The effect that change in one part of an ecosystem has on another, and how this effect then influences the source of the change by inducing more or less of it. Positive feedback is a circular path of effects that are self-reinforcing. When part of the system increases, another part of the system also changes in a way that makes the first part increase even more. Positive feedbacks are a source of instability and a strong driver of change as they can force the system outside of its normal operating boundaries (Kéfi, Holmgren, & Scheffer, 2016).

Heritability. A statistic used in the fields of breeding and genetics that estimates the proportion of variation in a phenotypic trait in a population, which is due to genetic variation between individuals in that population (Wray & Visscher, 2008).

Keystone species. A species on which other species in an ecosystem largely depend, such that if it was removed the ecosystem would change drastically (Paine, 1969).

Keystone-pathogen. A microbial species that supports and stabilizes disease by instigating inflammation (Hajishengallis et al., 2012).

Priority effects. The initial order and timing at which species disperse and colonize an empty community, which, in turn, alters how drift, selection, and diversification influence community assembly and succession (Fukami, 2015).

Prospective longitudinal study design. A study design that follows a set of subjects, which differ with respect to factors under study, over time to determine how these factors predict a specific outcome (Diggle, Liang, & Zeger, 2013).

Selection. In an ecological context, selection occurs when individuals of different species vary in their fitness and niche requirements, producing variation in reproduction and extinction rates between individuals and species (Vellend, 2016).

Speciation. The process by which new species arise in the course of evolution (Vellend, 2016).

Stability. There are many definitions of stability, some measuring the temporal variability of, for example, abundance or biomass over time, or some that measure responses to perturbations (see Box 2).

Steady state. If the state variables that are used to describe the state in a dynamical system are unchanged over time, the system is said to be in a steady state (Didier et al., 2018).

Time series data. A time series is a sequence of data points collected over time (Chatfield, 2013). In the microbiome, time series often represent microbial taxonomic or genic composition from the same host over multiple time points.

Time series analysis. Time series analysis encompasses a wide range of statistical methods for analyzing time series, including tests of temporal autocorrelation, Fourier and wavelet transforms to analyze frequencies, time series decomposition to extract seasonal, trend and noise components, and state-space models to retrospectively study the behavior of a system underlying the time series, or to make forecasts beyond the last observation (Chatfield, 2013; West & Harrison, 1989).

day to the next, with potential consequences for host physical functioning (e.g., Caporaso et al., 2011; David et al., 2014). Hence, the next frontier of gut microbiome research must consider time: Compared with cross-sectional studies, time series analyses of mammalian gut microbiomes from several subjects will yield deeper insights into the drivers of gut microbiome change and the consequences for host health and fitness. Time series analyses will be essential to forecast or predict microbiome change, connect microbiome dynamics to host health and fitness, learn the causal role that host environments and behaviors play in microbiome change, and understand the role of vertical transmission and historical

contingency in microbiome assembly. However, *time series data* on gut microbiomes, especially data sets that span multiple individual hosts, remain rare. Nearly all such data are collected on humans, which can be challenging and expensive study subjects: Dense time series and covariates that explain gut microbiome dynamics, such as diet and social interactions, are difficult to collect. As a result, most such data sets have either few subjects (e.g., Caporaso et al., 2011; David et al., 2014), or if they have more subjects, they have relatively few time points per subject, limiting their statistical power (e.g., Claesson et al., 2011; Faith et al., 2013; Flores et al., 2014). These discrepancies can lead to seemingly contradictory results; for

example, Caporaso et al. (2011) sampled two human adults daily for 15 months and found that each individual's gut microbiome exhibited high variability over time. In contrast, Faith et al. (2013) sampled 37 human adults 2–13 times (up to 296 weeks apart) and concluded that individuals' gut microbiomes were remarkably stable. However, these studies differed in the time scales over which they measured gut microbial dynamics (daily changes vs. weekly or monthly changes). As such, it is unclear which drivers explain gut microbiome dynamics at different time scales, and which of these dynamics are most relevant to host physiology, health, and fitness.

Primatologists can help overcome these barriers. One hallmark of field-based primatology is a focus on the behavior, ecology, physiology, and life histories of known individual animals. Indeed, primate field studies often collect long-term, individual-based data on the phenotypes of many subjects, sometimes from the animal's birth to death (Bronikowski et al., 2016; Clutton-Brock & Sheldon, 2010a, 2010b; Kappeler & Watts, 2012; Strier et al., 2010). Primate studies have long led the way in using longitudinal fecal sampling to characterize their subjects' genes (e.g., Morin, Wallis, Moore, Chakraborty, & Woodruff, 1993; Snyder-Mackler et al., 2016), hormones (e.g., Gesquiere, Altmann, Archie, & Alberts, 2018; Whitten, Brockman, & Stavisky, 1998), and parasites (e.g., Freeland, 1979; Müller-Klein et al., 2018; Stuart & Strier, 1995). Hence, such projects are well positioned to pair their wealth of long-term life history data with time series of individual subject's gut microbiomes. With this combination of data types, primatologists may be able to fill key gaps in microbiome dynamics that may be impossible to fill in humans or other animals, including our understanding of the processes governing microbiome assembly and succession, microbiome temporal dynamics and *stability*, and how these changes influence microbiome function and host health and fitness.

Our objective in this review is to summarize major unanswered questions about the mammalian gut microbiome that require time series data and where individual-based primate studies are well positioned to provide answers. We begin by introducing some of the major ecological processes governing gut microbiome assembly, dynamics, and stability. We then briefly summarize statistical challenges and approaches to microbiome time series analysis. We next highlight five diverse questions in microbiome science where primatology is poised to make contributions. Our goal is not to provide a comprehensive review of these questions, but rather to introduce key barriers to progress and explain how primate studies might overcome these barriers. The first four questions are united in that each addresses the factors and processes that drive gut microbial change over time: (a) Do early life events shape gut microbiome composition in adulthood? (b) Do shifting social landscapes cause gut microbial change? (c) Are microbiome phenotypes heritable across variable environments? And (d) does the gut microbiome show signs of host aging? Finally, the fifth question addresses how longitudinal microbiome data sets can be used to understand the functional consequences of gut microbiome change by asking, (e) do gut microbiome composition and dynamics predict host health and fitness? Tackling these questions will greatly improve

our understanding of both the processes shaping the gut microbiome over time and the consequences of these changes for primate hosts. Such research is also likely to reveal unanticipated discoveries, raising completely new questions for primatologists, microbiologists, ecologists, and evolutionary biologists. While our review largely focuses on 16S rRNA amplicon sequencing data, the research questions we review remain equally relevant for data generated with other “-omics” approaches such as transcriptomics, proteomics, and metabolomics.

2 | WHAT ECOLOGICAL PROCESSES CONTRIBUTE TO GUT MICROBIOME ASSEMBLY, TEMPORAL DYNAMICS, AND STABILITY?

To date, a handful of papers have explored the temporal dynamics of primate gut microbiomes, revealing considerable dynamism. For instance over developmental scales, different lemur species exhibit different patterns of infant gut microbial succession, and these successional differences are linked to differences in lemur gut morphology and dietary regimes (McKenney, Rodrigo, & Yoder, 2015). Over seasonal time scales, the gut microbiomes of wild gorillas (*Gorilla gorilla gorilla*) and chimpanzees (*Pan troglodytes troglodytes*) fluctuate with rainfall, mirroring the apes' switch from fiber-rich leaves and bark to succulent fruits (Hicks et al., 2018). Over even shorter time scales, Ren, Grieneisen, Alberts, Archie, and Wu (2016) found considerable differences in baboon (*Papio cynocephalus*) gut microbiome composition from 1 day to the next: Gut microbiomes sampled from the same baboon a few days apart were just as different as microbiomes sampled from that animal 10 years apart. While these studies suggest that the gut microbiomes of non-human primates change in different ways over different time periods and across life, few studies have used existing ecological frameworks to understand the processes that drive these changes.

Community ecology offers many theories and processes to understand gut microbiome dynamics (e.g., Costello, Stagaman, Dethlefsen, Bohannan, & Relman, 2012; Koskella, Hall, & Metcalf, 2017; McKenney et al., 2018; Sprockett, Fukami, & Relman, 2018; Walter & Ley, 2011). Ecological communities are examples of *complex adaptive systems* where large-scale patterns such as diversity-stability, diversity-productivity, and species-energy relationships emerge from interactions among species (Preston, 1948; Levin, 1998). They are also examples of *dynamical systems* that result from species interactions unfolding over time to produce complex dynamics such as periodicities, chaos, or *alternative stable states* (May, 1975, 1977). The basic principles guiding community dynamics can be summarized in four overarching processes that parallel well-known processes in evolution: *dispersal*, *selection*, *drift*, and *speciation* (Vellend, 2016; Vellend & Agrawal, 2010). In ecological terms, speciation generates new species, while dispersal, drift, and selection shape the relative abundances of those species and their loss from communities over time (Vellend, 2016; Vellend & Agrawal, 2010).

The development of ecological theory has significantly increased our understanding of (a) how these processes affect community composition and dynamics, (b) when certain processes dominate, and (c) how they can combine to produce complex interacting effects. For instance, the theory of island biogeography focuses on the balance between dispersal and drift (MacArthur & Wilson, 1967). This theory explains how species richness increases with island size and the distance from the mainland: The size of an island influences the colonization and extinction rates, and thus indirectly biodiversity. Island biogeography combined with the neutral theory of molecular evolution was later used to develop the unified neutral theory of biodiversity, which also aims to explain the diversity and relative abundance of species in ecological communities. Neutral theory makes the simple assumption that ecologically similar species in a community are demographically equivalent, such that individuals interact with and experience each other as though they were exactly the same regardless of traits and adaptations (Hubbell, 2001). Owing to its simplicity, neutral theory has had a tremendous impact on our understanding of the role of dispersal, drift, and speciation versus niche-based differences for determining biodiversity. Finally, building on these theories, metacommunity theory has become a new cornerstone of ecology, aiming to explain how species interactions at different temporal and spatial scales work together with dispersal to shape local and regional community composition and dynamics (Leibold et al., 2004). Metacommunity theory can be divided into four paradigms that can be positioned along a continuum ranging from niche-based to neutral processes: patch-dynamic, species sorting, mass-effect, and neutral, each capturing different processes affecting metacommunity dynamics. At one extreme, variation in the metacommunity is determined by the responses of different species to environmental gradients; and at the other extreme, individuals are assumed to be identical in their fitness, and variation in community composition is mainly driven by drift (Leibold et al., 2004).

Below, we review cases from the microbiome literature where these processes either independently or in combination have been adopted to explain microbiome change over time.

Dispersal is the movement of individuals across space. The effect of dispersal on community dynamics depends on the number and composition of dispersing individuals relative to the size and composition of the recipient community. In animal microbiomes, microbial dispersal may increase gut microbial similarity between hosts that share habitat or have high rates of physical contact with each other. For instance, in controlled experiments, Burns et al. (2017) found that microbial dispersal between zebrafish homogenized the intestinal microbiome of co-housed host pairs, eliminating microbiome differences linked to host strains. In humans, people are constantly over-writing each other's microbial fingerprints in the built environment. For example, families that moved to a new house replaced the past owner's microbial fingerprint with their own within 24 hr (Lax et al., 2014). The effects of dispersal on gut microbiome community dynamics also depend on the spatial scale considered. A study of mammal species across the Americas found that gut microbiome similarity decayed with increasing geographic distance

between species, suggesting that dispersal limitation of microbial taxa can lead to diversification of microbial lineages between host populations (Moeller et al., 2017). Similar effects may explain why sympatric gorillas (*Gorilla gorilla gorilla*) and chimpanzees (*P. troglodytes troglodytes*) exhibit similar gut microbiomes (Moeller et al., 2013). On smaller spatial scales, direct contact between hosts facilitates microbial dispersal and homogenization of microbiomes both within and between host species (Amato et al., 2017; Grieneisen, Livermore, Alberts, Tung, & Archie, 2017; Lax et al., 2014; Moeller, Foerster, et al., 2016; Moeller et al., 2017; Song et al., 2013; Tung et al., 2015).

Ecological selection shapes community composition when different species vary in their fitness and niche requirements, producing species-level variation in reproduction and extinction rates. In animal microbiomes, selective processes may partly explain differences in gut microbiome composition linked to host age, diet, and habitat because all of these factors could contribute to differential survival and reproduction of gut microbial species or strains, either inside or outside of hosts. For instance, outside of a host, differences in the climate, soils, and vegetation affect which microbes survive in the environment, and in turn, which microbes have the opportunity to colonize a primate's intestinal tract (this process is also known as species sorting; Székely & Langenheder, 2014). Within the host, across developmental time scales, microbial selection is thought to increase from early life to adulthood, partly due to physiochemical maturation of the gut, but also because hosts become more effective at curating their microbiomes (figure 2; Burns et al., 2015; Dini-Andreote & Raaijmakers, 2018). Dietary regimes and gut morphology also represent strong selective forces (David et al., 2013; Groussin et al., 2017; Ley et al., 2008; McKenney et al., 2015). This is because dietary changes affect gut contents, leading to differential growth and survival among gut microbial species, and thus different gut microbiome compositions (David et al., 2013). Selection, in combination with dispersal, may explain why gut microbial composition differs between captive and wild primates (Clayton et al., 2016). Specifically, changes in diet (e.g., the loss of dietary fiber) and in the environment (e.g., from a forest to a cage) affect both the selective regimes affecting on the gut microbiome, as well as which microbes hosts are exposed to (Clayton et al., 2016).

Drift arises from random changes in species relative abundances due to stochastic birth and death events (Hubbell, 2001). In a hypothetical scenario where all individuals live in a closed community (i.e., no immigration and dispersal), and all individuals are demographically identical, drift is the only process affecting community dynamics (Vellend & Agrawal, 2010). Drift is stronger in small populations, thus it represents an important process affecting local species extinctions. For example, rare gut microbes that are perturbed by antibiotics or illness should be more prone to extinction than more abundant microbes (Dethlefsen & Relman, 2011; Fukuyama et al., 2017). The effects of drift on animal microbiomes are not well understood, partly because it is difficult to tease apart drift from selection and dispersal. However, Burns et al. (2015) found in an experimental zebrafish system that drift and dispersal

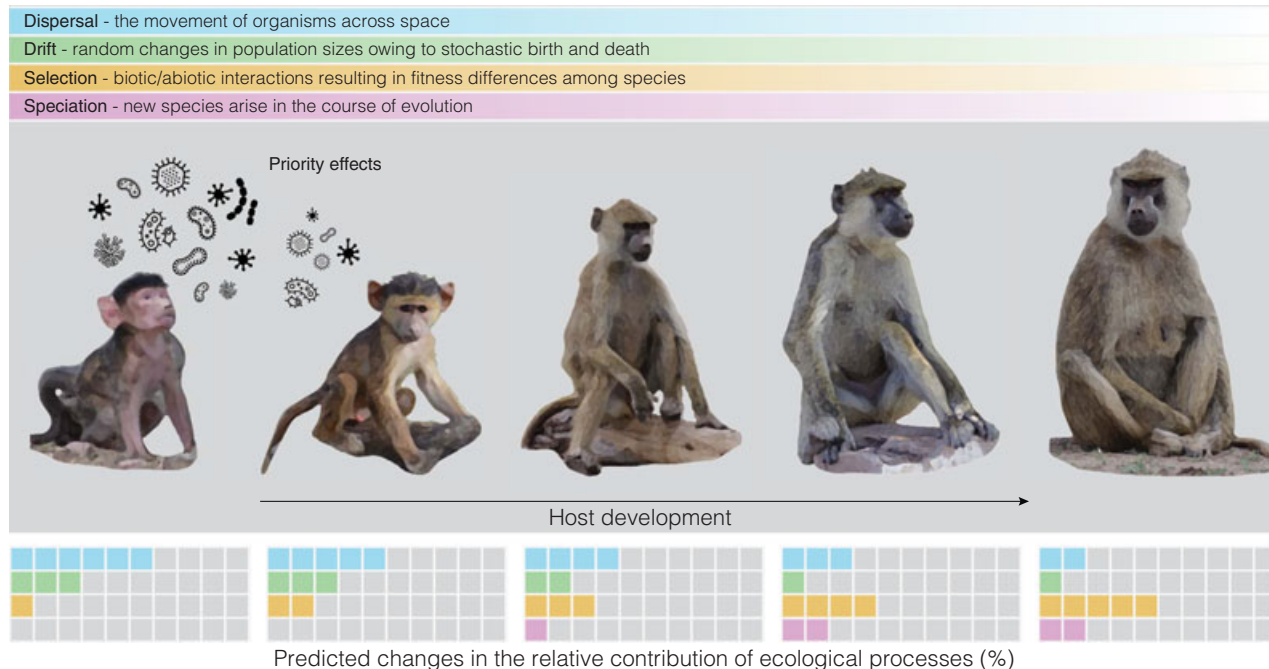


FIGURE 2 Conceptual figure depicting the relative contribution of the four ecological processes that govern community dynamics across primate development. In infants, drift and dispersal determine early colonizing microbes, which create priority effects that are thought to have a large influence on subsequent microbial colonization. As the host develops and matures, selection is expected to increase as the physicochemical conditions of the gut stabilize, and as hosts become more effective at curating their microbiomes. As microbial species persist across host development, the chances for speciation increase; hence speciation may play a stronger role in adult microbiomes as compared with infants and young juveniles. Figure adapted from Dini-Andreote and Raaijmakers (2018)

dominated in newly hatched larvae, but were less important as the hosts developed and matured, perhaps because of increasing host control over the microbiome and hence stronger selective forces (Figure 2).

Speciation is the process by which new species arise in the course of evolution. Speciation can, therefore, shape the regional distribution of species, and in turn, local community composition and dynamics (Vellend, 2016). Because microbes have short generation times, speciation has the potential to shape animal microbiomes over animal lifespans, especially in long-lived primates (Figure 2). Indeed, Koeppl et al. (2013) found that in lab conditions, microbial speciation can occur over the course of a few days. Speciation may partly explain why allopatric populations of chimpanzees (*P. troglodytes troglodytes*) and gorillas (*G. gorilla gorilla*) harbor divergent gut microbiomes compared with sympatric host populations (Moeller et al., 2013). Specifically, while some of this divergence is likely due to selective processes created by site-specific diets and low rates of microbial dispersal between allopatric host populations, microbes can rapidly diversify and adapt when faced with strong selective pressures (Koeppl et al., 2013). Furthermore, when there is strong partner fidelity, microbes and their hosts may speciate in parallel. For example, the bacterial families *Bacteroidaceae* and *Bifidobacteriaceae* have diversified in concert with hominid hosts, including humans (Moeller, Caro-Quintero, et al., 2016).

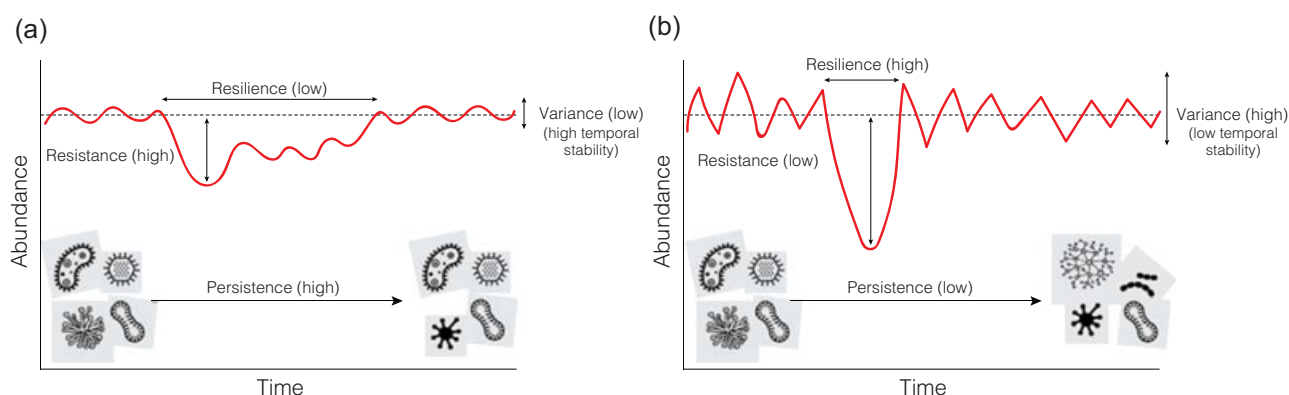
These four processes—dispersal, selection, drift, and speciation—interact to produce complex community patterning across space and

time. While it is not possible to review all of the relevant interactions and processes relevant to gut microbiome dynamics, below we summarize a few phenomena that have been especially influential in understanding microbiome dynamics, including *priority effects*, *alternative stable states*, *feedback loops*, and *keystone species*.

In priority effects, the order and timing of species arrivals determine the composition and dynamics of current ecological communities (Fukami, 2015). A newborn infant, for instance, represents a blank canvas ready to be colonized by microbes via dispersal. However, which microbes arrive first determines the identity and the order that later microbial immigrants are able to colonize (Didier, Katharine, Leo, & Karoline, 2018; Fukami, 2015). This is because first-arriving microbes fill particular niches by quickly reaching carrying capacity, while simultaneously modifying the gut in their favor, thereby altering the ability of subsequent microbial immigrants to colonize (Sprockett et al., 2018). Such priority effects can also have long-term consequences for overall microbiome stability (see Box 2 for definitions of ecological stability), and may adversely affect host health and fitness later in life (see Sections 4.1 and 4.5). Subtle differences in the arrival order of species may shift communities into *alternative stable states* (Didier et al., 2018; Fukami, 2015). A switch in diet, for instance, can alter the nutritional niche of the gut, thus favoring the growth of pathogens at the expense of commensal microbes (Chen et al., 2017). However, the gut microbiome can also display resilience (see Box 2) and recover its initial state following a perturbation (see Box 2; Faust, Lahti, Gonze, de Vos,

BOX 2 Ecological stability

Stability is often proposed as a measure of microbiome health and hence host health (see also Sections 4.4 and 4.5). However, ecological stability is a multifaceted concept that encompasses both variability over time and response to perturbations; it can, therefore, be measured in multiple ways (see Figure below; Donohue et al., 2016). Facets of ecological stability that are particularly relevant to gut microbiomes include resilience, resistance, persistence, and temporal stability. While resistance is the degree to which a gut microbiome is able to withstand change following a perturbation (e.g., antibiotics or illness), resilience is the rate at which it returns to the initial steady state, or moves to a new alternative stable state (Pimm, 1984). Microbiomes with faster return times are said to be more resilient than those recovering more slowly. Persistence is the length of time the microbiome maintains the same microbial composition (Pimm, 1991); it can also be defined as a “core” of microbial species persisting beyond some arbitrarily defined threshold of time (Björk, O’Hara, Ribes, Coma, & Montoya,). The most applicable measure of ecological stability that can be directly computed on time series is temporal stability (S_i), which is defined as the ratio of the mean abundance (μ_i) of the i th microbial species to its standard deviation (σ_i) calculated across the time series (Tilman, 1999). See Didier et al. (2018), Donohue et al. (2016) for more facets of ecological stability.



The multifaceted nature of ecological stability. In scenario (A), a gut microbiome shows a high resistance but low resilience following a perturbation. It also has a high persistence, and low variance (i.e., high temporal stability). In scenario (B), another gut microbiome shows the opposite patterns. The horizontal dashed lines depict the steady state, which can be computed as the long-term average abundance before any perturbation. The Y-axes show the aggregated abundance of the gut microbiomes, and the X-axes depict time. Figure adapted from Donohue et al. (2016).

& Raes, 2015). For example, David et al. (2014) found that when one healthy adult human traveled abroad for several weeks and underwent a major dietary change, the ratio between the two dominant groups of bacteria in the gut increased nearly twofold, but reverted to its initial ratio after returning home. We currently know very little about what makes a microbiome more resilient. What is clear is that resilience is an emergent property that applies in different ways in different subjects and in the various functional layers that make up the microbiome (figure 1; Bäckhed et al., 2015; Gerber, 2014; Hollister, Gao, & Versalovic, 2014).

At their core, alternative stable states result from positive species interactions and feedback loops (Kéfi, Holmgren, & Scheffer, 2016). For instance, strong cooperation between microbes may destabilize the gut microbiome because positive interactions induce species coupling and positive feedback: if one microbe decreases in abundance, it will drag other species down with it and cause community collapse (Coyte, Schluter, & Foster, 2015). In contrast, species that respond differently to biotic and abiotic conditions fluctuate asynchronously over time (figure 3; Loreau, 2010). These asynchronous fluctuations are expected to increase microbiome

stability as one species' sharp decline is compensated by another's increase. This is one reason, for example, why community stability tends to increase with species diversity (figure 3; Loreau, 2010). The above findings further point to the possibility of commensal keystone species, which have a disproportionate negative effect on the microbiome upon their removal (Berry & Widder, 2014; Fisher & Mehta, 2014). However, once the microbiome has been destabilized, alternative stable states associated with dysfunction may be reached by *keystone-pathogens*—microbes supporting and stabilizing disease by instigating inflammation (Hajishengallis, Darveau, & Curtis, 2012).

Together, the basic ecological forces—dispersal, selection, drift, and speciation—and the processes that emerge from them (e.g., alternative stable states, keystone species, etc.) have been important in shaping scientific thinking about the forces underlying microbiome dynamics. However, it is important to note that these ecological frameworks were developed for free-living, macrocommunities. Microbial communities, including the gut microbiome, differ from these communities in several important ways: (a) gut microbiome diversity is astonishing, and functional redundancy is probably much more common in microbiomes than in free-living communities;

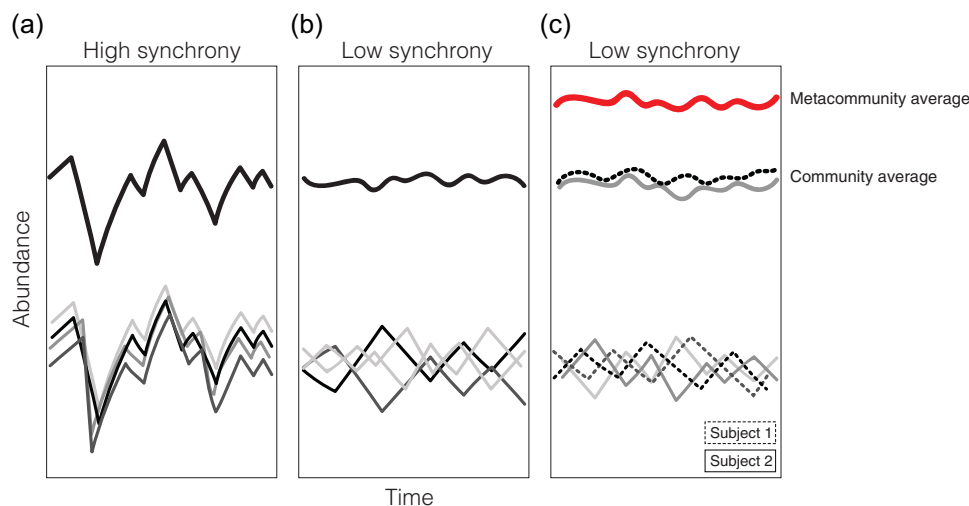


FIGURE 3 The relationship between species synchrony and stability at higher levels. (a) Depicts a scenario where gut microbes in a single host, indicated by the thin black and gray lines, respond similarly to biotic and abiotic fluctuations in the gut, which leads to higher instability at the microbiome community level (thick black line). (b) Depicts the opposite scenario where gut microbes in a single host respond differently to biotic and abiotic fluctuations in the gut, which in turn, leads to a higher stability at the microbiome community level. (c) is similar to (b), but the plot shows microbes and the microbiome community in two different host subjects (depicted using dashed and solid lines). Again, asynchronous species fluctuations lead to a higher stability at the microbiome level for both hosts, which in turn, lead to a higher stability at the social group level (i.e., metacommunity level; thick red line). The Y-axes show abundance and the X-axes time. Figure adapted from Wilcox et al. (2017)

(b) microbes can disperse both horizontally and vertically, with implications for the evolutionary outcome of host-microbe interactions; (c) unlike free-living communities, microbiome dynamics are, to some extent governed by the host, introducing a completely new selective force; and (d) microbes regularly exchange genes via lateral gene transfer; hence microbes can take on functions from their neighbors. These important differences between free-living macro-communities and host-associated microbial communities mean that there is an urgent need to develop ecological theory that is specific to the microbiome. Importantly, microbes' short generation times and small genomes blur the line between ecological and evolutionary processes and time scales.

3 | TIME SERIES ANALYSIS APPROACHES FOR MICROBIOME DATA

Time series analysis encompasses a wide range of statistical methods and models that are often not trivial to apply without some expert knowledge (see e.g., Chatfield, 2013; Faust et al., 2015). Many of the simplest methods require that the time steps between samples are equidistant, which can be challenging to achieve when fecal samples are collected opportunistically. Moreover, microbiome data exhibits several undesirable characteristics that must be considered in the analysis. Most of these characteristics are related to how the data are generated (see e.g., Silverman, Shenav, Halperin, Mukherjee, & David, 2018). First, high-throughput DNA sequencing produces proportions of counts per operational taxonomic unit (OTU, a placeholder for taxon) per sample that is constrained by an arbitrary sum imposed by the sequencing platform (this characteristic is referred to as compositionality; Gloor, Macklaim, Pawlowsky-Glahn, & Egozcue, 2017). This

property limits inference to relative abundances, and introduces uncertainty in the estimates of those relative measurements (Gloor et al., 2017). Second, high-throughput DNA sequencing often produces extremely sparse counts; that is, much of the data consists of zero values that can arise due to multiple processes. For example, an OTU can have zero abundance because it is completely absent from a sample, or because its abundance falls below the detection limit of the sequencing platform (Silverman, Roche, Mukherjee, & David, 2018). Third, because microbial diversity is exceptionally high in many biological environments, the generated count table is high-dimensional, with hundreds to thousands of OTUs that can make inference computationally hard or even impossible without additional filtering steps. While it is challenging to account for all these data characteristics in the analysis, failure to do so can lead to spurious correlations between microbes and misleading results (Gloor et al., 2017; Tsilimigras & Fodor, 2016). To tackle the compositional property, data transformations or compositionally robust methods should be used (see e.g., Gloor et al., 2017; Lovell, Pawlowsky-Glahn, Egozcue, Marguerat, & Bähler, 2015; Weiss et al., 2016).

Owing to the nontrivial nature of time series analysis, and the many undesirable characteristics of microbiome data, there has been a growing interest in developing easy-to-use longitudinal time series methods, such as MetaLonDa (Metagenomics Longitudinal Differential Abundance) to identify significant time intervals of differentially abundant microbial taxa (Metwally et al., 2018), and TIME (Temporal Insights into Microbial Ecology), a web based framework that offers popular time series analyses, including Dickey-Fuller tests to calculate time series stationarity, Granger causality to find causal relationships between taxa, and dynamic time warping to measure the displacement between two time series (Baksi, Kuntal, & Mande,

BOX 3 State-space models for microbiomes: future directions

State-space models (SSMs) differ from, for example, linear mixed models in that they assume there is an unobservable Markov chain called the “state process”, and that the observed time series is an imprecise measurement of that process (see Equations (1) and (2)). A growing number of SSMs are being developed for microbiome applications, including models that address the technical challenges of microbiome data (e.g., Gibson & Gerber, ; Ridenhour et al., 2017; Silverman, Durand, et al., 2018), or infer microbe-microbe interactions (see e.g., Chen et al., 2017; Fisher & Mehta, 2014; Trosvik & de Muinck, 2015). Here we (a) showcase a simple SSM, and (b) briefly discuss advancements that are needed to answer some of the questions posed in this review. For simplicity, we do not explicitly show how to account for the several undesirable microbiome data characteristics that were mentioned in Section 3 (here we refer interested readers to e.g., Gibson & Gerber, ; Ridenhour et al., 2017; Silverman, Durand, et al., 2018; Warton et al., 2015).

Let $Y_{t,d}$ denote a time series with the number of counts observed for operational taxonomic unit $d \in \{1, \dots, D\}$ in time point $t \in \{1, \dots, T\}$. In the simplest case, samples Y_t are assumed to be independent and identically normally distributed as $(Y_t|\theta) \sim \mathcal{N}(\theta, V)$, where V reflects the measurement error. However, as the microbiome state θ can change both gradually, for instance with season, or more abruptly, for instance during illness, a time-varying state can easily be incorporated, such that

$$Y_t \sim F_t \theta_t + \nu_t, \quad \nu_t \sim \mathcal{N}(0, V_t) \quad (\text{Observation equation}), \quad (1)$$

where F_t is a vector of time-varying covariates, with the state vector $\theta_1, \dots, \theta_t, \dots, \theta_T$ representing the underlying microbiome dynamics in the time series, and ν_t describing random fluctuations arising from measurement error. The underlying time evolution is further modeled as a simple random walk such that the microbiome state in time t depends on the previous state in time $t - 1$,

$$\theta_t = G_t \theta_{t-1} + \omega_t, \quad \omega_t \sim \mathcal{N}(0, W_t) \quad (\text{State equation}), \quad (2)$$

where G_t represents the state matrix describing the dynamics of the microbiome state in the previous time θ_{t-1} , and ω_t corresponds to unpredictable changes in the dynamics between time $t - 1$ and t . Which lag to use can be determined from the partial autocorrelation function (see Chatfield, 2013 for more information).

Depending on the exact specification of the system matrices (F_t and G_t) and the covariance matrices (V_t and W_t), different types of models can be specified, such as, for example, static and dynamic mixed effects models, and models with seasonal or polynomial trends (West & Harrison, 1989). For simplicity, Equations (1) and (2) only model *one* time series from *one* host; however, to answer many of the questions we pose in this review, these equations have to be expanded to model concurrent microbiome time series from multiple hosts (see e.g., Silverman, Durand, et al., 2018). While time-varying covariates such as, for example, diet and rainfall, can already be modeled in Equation (1), new challenges include how to accommodate for more complex covariates in the state-space framework, such as hosts' social interactions and genetic relatedness. Such covariates can, similar to species phylogenies, be modeled in static linear mixed models (see e.g., Björk et al., 2018; Ives & Helmus, 2011). However, to answer questions regarding how, for example, changes in microbiomes over time can be attributed to a shifting social landscape (Section 4.2), or whether microbiome phenotypes are repeatable over time (Section 4.3), time series models, such as SSMs are necessary.

2018). While these methods are valuable to the field, they are limited in their applicability and scope, and many of the questions we introduce in this review will require greater flexibility. In Box 3, we give a brief introduction to state-space models (SSMs), which play a central role in time series analysis. They are typically used to retrospectively study the behavior of a system underlying a series of observations, or to make forecasts beyond the last observation (West & Harrison, 1989). Because SSMs model observation error separately from the underlying “state” of the system, they can successfully describe a system's dynamics and its response to different inputs. An important feature of SSMs is that they do not require time series to be stationary (i.e., statistical properties such as mean, variance, and autocorrelation does not need to be constant over time), and they are therefore not sensitive to nonlinear relationships (West & Harrison, 1989). Similar to generalized linear mixed models, SSMs can also handle non-normal data, and account for fixed and random

effects. This flexibility means that SSMs are likely to become a cornerstone of longitudinal time series analysis for microbiome data.

4 | KEY AREAS OF MICROBIOME SCIENCE WHERE PRIMATE STUDIES CAN CONTRIBUTE

Building on the ecological processes described above, here we briefly review five diverse but fundamental questions in microbiome science that require time series data from multiple hosts, and where individual-based primate studies are especially well positioned to provide answers. The first four questions address drivers of microbiome change over time. The fifth question addresses the consequences of microbiome change for hosts. Our goal is not to provide a thorough review of each topic; rather we introduce a

handful of recent studies in each area, discuss key barriers or gaps to answering these questions, and focus how primate studies can help overcome these barriers and contribute to answering the question.

4.1 | Do early life events shape gut microbiome composition in adulthood?

Events early in life can have profound consequences for an animal's life history, health, and fitness (Berens, Jensen, & Nelson, 2017; Chaby, 2016; Lindström, 1999). An emerging body of work suggests that early life effects may also shape or be mediated by animal microbiomes (Berger, Lemaître, Allainé, Gaillard, & Cohas, 2018; Clarke, 2014; Laforest-Lapointe & Arrieta, 2017; Martínez et al., 2018). The suitability of primate systems for understanding these processes stems from primatology's traditional focus on individual-based research, and its long history of studying early life effects—especially maternal effects (e.g., Altmann & Alberts, 2005; Bailey, Lubach, & Coe, 2004; Bernstein, Setchell, Verrier, & Knapp, 2012). Such research has found that diverse maternal effects, ranging from a mother's rank and cortisol levels to the quality of offspring care and social connectedness, can affect diverse offspring phenotypes, including temperament (Suarez-Jimenez et al., 2013), lifespan (Silk et al., 2009), adult cortisol (Onyango, Gesquiere, Wango, Alberts, & Altmann, 2008), mating success (Surbeck, Mundry, & Hohmann, 2010), immune function, and motor skill acquisition (Berghänel, Heistermann, Schülke, & Ostner, 2016).

Whether these early life effects also shape primate gut microbiomes is unknown, but this possibility is supported by two main lines of evidence. First, as discussed in Section 2, events early in the formation of the gut microbiome may have consequences for subsequent community assembly, dynamics, and stability (Fukami, 2015; Sprockett et al., 2018). In support, there is considerable evidence for priority effects in human microbial development. For example, birth method can determine the initial state of the human gut microbiome and its subsequent assembly (Bäckhed et al., 2015; Dominguez-Bello et al., 2010; Goedert, Hua, Yu, & Shi, 2014; Yassour et al., 2016). Indeed, Chu et al. (2017) found that infants delivered by cesarean section shared more microbes with their mothers' skin at the time of birth than infants delivered vaginally. Cesarean infants have also been found to lack the bacterial genera *Bacteroides* and *Bifidobacterium*, which are largely responsible for the breakdown of oligosaccharides in breast milk, and these effects can persist for at least 6–18 months after delivery (Bäckhed et al., 2015; Korpela et al., 2018; Yassour et al., 2016). Beyond delivery mode, malnutrition can also affect gut microbial development. Acute malnutrition in early life has been found to keep the gut microbiome in a state of persistent immaturity (M. I. Smith et al., 2013; Subramanian et al., 2014). To test whether improved nutrition can rescue an “immature” gut, Subramanian et al. (2014) administered nutritional interventions and found that infants' guts returned to their initial “immature” state after the intervention. These studies expose the major gaps in the literature—little is known about how long early life effects on the gut microbiome persist, or whether humans are representative of other host-associated microbial systems, such as non-human primates.

The second line of evidence is that the early life effects we already know about in primates could be relevant to gut microbiome assembly and development, including the quality of maternal care, dominance rank, social environment, and harsh conditions such as drought. For instance, in The Gambia, people born during the “hungry season” exhibit much higher mortality in adulthood as compared with those born during the “harvest season” (Moore et al., 1997, 2004). Because many non-human primates also live in seasonal environments, and because seasonal effects have been demonstrated on primate microbiomes (Hicks et al., 2018; Sun et al., 2018; Trosvik et al., 2018), non-human primates may be useful for understanding early life effects on gut microbially mediated forms of nutritional programming, or the process through which variation in nutrition affects individual development (Langley-Evans, 2009). While long-term effects like these have not yet been shown in non-human primates, there is abundant evidence that factors like stress and rank shape microbiome composition over short-time scales. For example, working in captive rhesus macaques (*Macaca mulatta*), Bailey, Lubach, and Coe (2004) demonstrated that maternal stress during pregnancy altered infant gut microbiomes across the first 24 weeks of life. In wild primates, social status is sometimes linked to maternal stress (Markham et al., 2014; Murray et al., 2018); hence, maternal rank may also shape the infant's gut microbiome in natural populations. In non-human primates, new evidence strongly suggests that diet and social environment are important influences of gut microbial composition (Amato et al., 2017; Bennett et al., 2016; Grieneisen et al., 2017; Hale et al., 2018; Moeller, Foerster, et al., 2016; Perofsky, Lewis, Abondano, DiFiore, & Meyers, 2017; Tung et al., 2015). However, no studies have yet studied the effects of social isolation or nutrient limitation on the gut microbiome's of wild primates during early life.

Together, these lines of evidence suggest that early life events could be important in shaping non-human primate gut microbiomes through the juvenile period and into adulthood. Primate hosts with relatively short generation times and lifespans may be particularly useful because of the relative ease of connecting early life events to later-life outcomes in such species. Primate species where it is easy to collect longitudinal samples shortly after birth will also be essential to understand heterogeneity in the initial stages of gut microbial development. Major unanswered questions include: How do hosts, their environments, and ecological processes interact to produce early life effects on gut microbiomes? How long do these effects persist? And, what are the consequences of these effects for host physical functioning in adulthood? These questions are important in a wide variety of systems, and primatologists that are able to collect fecal samples from the same animal in early life and adulthood are well positioned to provide answers.

4.2 | Does a shifting social landscape cause gut microbiome change?

To date, cross-sectional research on humans and non-human primates has been at the forefront of understanding how an individual's social context may shape its gut microbiome (Amato

et al., 2017; Bennett et al., 2016; Lax et al., 2014; Moeller, Foerster, et al., 2016; Perofsky et al., 2017; Song et al., 2013; Tung et al., 2015). For instance, recent cross-sectional analyses of wild baboons (*P. cynocephalus*), chimpanzees (*P. troglodytes troglodytes*), howler monkeys (*Alouatta pigra*), and lemurs all found that individuals who spend more time in contact or in close proximity to each other have more similar gut microbial compositions than individuals who are not in contact or do not live together (Amato et al., 2017; Moeller, Foerster, et al., 2016; Perofsky et al., 2017; Tung et al., 2015). Taking a longitudinal perspective on this phenomenon will help move the field forward in three important ways. First, longitudinal data coupled with time series analysis will be essential to tease apart the effects of social interactions from other aspects of group living, such as shared environments, similar diets, and host genetic relatedness (see also Section 4.3). Second, the structure of social networks strongly affects the rate at which infectious diseases spread through host populations (Watts & Strogatz, 1998), and microbes likely spread via these same pathways. Primate studies with densely sampled social networks, in combination with microbial strain tracking, could be used to learn how microbial strains, both commensal and pathogenic, propagate through primate societies. Third, taking a metacommunity perspective by treating subjects' gut microbiomes as local communities, connected by socially-mediated microbial dispersal, will allow primate studies to test current predictions of how of ecological processes contribute toward the stability of each local community, and how this in turn influences the stability at the metacommunity level (e.g., at the social group level).

With respect to the first advance, the multiple, concurrent effects of group living and social interactions that influence gut microbiome composition are difficult to decouple in cross-sectional studies. To date, most such studies attempt isolate the direct effects of microbial transmission between social partners by statistically accounting for correlates and confounds, for instance by controlling for dietary similarity, kinship, and shared environments (Grieneisen et al., 2017; Tung et al., 2015). As a result, there has been a growing interest in developing statistical models to account for complex covariates such as the host species phylogeny (Björk, Hui, O'Hara, & Montoya, 2018) or experimental design (Grantham, Reich, Borer, & Gross, 2017) in cross-sectional microbiome data sets. While similar statistical models for longitudinal time series data are rare (but see Laitinen & Lahti, 2018; Ridenhour et al., 2017; Silverman, Durand, Bloom, Mukherjee, & David, 2018), time series analyses on multiple, coresident primates will be essential to decompose variance into sources that directly reflect the myriad contributions of group living and social interactions in each moment of time. This is because different hosts living together in the same group, and even the same host over time, may be influenced by multiple factors at the same time. For instance, while host subject A's microbiome may, at time *t*, be largely governed by social interactions because this individual was highly socially connected, host subject B's microbiome may be largely explained by diet because this individual was socially isolated. Longitudinal data coupled with new statistical models (e.g., modifications of SSMs, see Box 3) will be essential to attribute variance to different factors

driving microbiome change and to decouple the direct effects of social interactions from the many correlates and confounds of social relationships and group living.

With respect to the second advance, longitudinal analyses offer more direct approaches for testing the role of microbial dispersal between social partners by tracking the spread of microbial strains within socially structured populations over time. Just as disease ecologists use time series data to trace the appearance of new infectious diseases within populations (see e.g., Craft, Volz, Packer, & Meyers, 2010; Eames, 2007), primate studies could combine strain tracking procedures (Brito & Alm, 2016; Morowitz et al., 2011; Nayfach, Rodriguez-Mueller, Garud, & Pollard, 2016; Oh et al., 2014; Smillie et al., 2018) with information on social networks and events that rewire these networks (e.g., fission or fusion of social groups, births and deaths, and sex-biased dispersal) to identify microbial strains of interest (e.g., commensal and/or pathogenic) and to test whether the network position of an infected host predicts the rate at which those strains colonize other hosts. In non-human primates that live in fission-fusion societies (Aureli et al., 2008), the dynamics of social networks could be leveraged to test predictions about the role of physical contact and proximity in strain sharing. While strain tracking is sometimes attempted with 16S rRNA sequencing data (Knights et al., 2011), these data often lack the phylogenetic resolution to truly trace microbial transmission at the strain level. Hence, we advocate the use population genetics approaches to measure microbial migration or dispersal between hosts. Such approaches rely on identity by common descent and require more extensive genetic data, generated by either shotgun metagenomic sequencing or whole microbial genome sequencing from cultured microbes (Asnicar et al., 2017; Smillie et al., 2018). These methods are becoming increasingly common and affordable and have been used to follow the establishment of microbes in the human gut after fecal transplant (Smillie et al., 2018) or trace vertical microbial transmission between mothers and infants (Asnicar et al., 2017; Smillie et al., 2018).

With respect to the third advance, time series data on multiple hosts will be essential to apply metacommunity theory to understand social effects on primate microbiomes at multiple scales. The microbiomes of individual subjects can be considered local communities connected by microbial dispersal, which is mediated by host social interactions. This perspective could be useful, for example, to learn how stability at the local level scales up to the metacommunity level (host social groups or populations; Figure 2). Local communities differ in how they respond to environmental fluctuations, such as rain and drought. How much local communities vary with respect to one another determines the level of synchrony at the metacommunity level. Just as low synchrony among species stabilizes local communities (Figure 3a,b; Loreau, 2010), asynchrony among local communities can increase stability at the metacommunity level (Figure 3c; Wilcox et al., 2017). A recent analysis on the colony forming Egyptian fruit bat found that while temporal changes in the fur microbiome were best described at the colony rather than the individual level, this was not the case for the gut microbiome (Kolodny et al., 2019).

Perhaps the common finding of strong individual signatures in the gut microbiome of humans and other animals reflects a low degree of synchrony, which may be critical for metacommunity stability and functioning. Overall, how the fluctuations of microbiomes in individual hosts contribute to stability and functioning of the gut microbiome at higher levels, including families, social groups, and populations, is completely unknown.

4.3 | Are gut microbiome phenotypes heritable across dynamic environments?

In humans, host genetic variation predicts microbiome composition, and microbe-by-host genotype associations predict health outcomes (Blekhman et al., 2015; Goodrich, Davenport, Clark, & Ley, 2017). Likewise in non-human primates, host genetic effects may explain the existence of host species-specific gut microbiomes (Amato et al., 2016; Moeller et al., 2014; Yildirim et al., 2010), and the observation that gut microbial similarity recapitulates host phylogenetic relationships (Moeller, Caro-Quintero, et al., 2016; Ochman et al., 2010). However, host and environmental factors, such as diet, social behavior, and season, may also play a strong role in creating these patterns (Bailey et al., 2011; Yatsunenko et al., 2012). Indeed, sympatric primate species have more similar microbiomes than allopatric species (McCord et al., 2014; Moeller et al., 2013), and species-specific microbiomes are absent in at least one primate hybrid zone (Grieneisen et al., 2018). Results like these highlight a key challenge: how do we measure microbiome *heritability*? That is, how do we disentangle host genetic effects from environmental effects on microbiomes in natural primate populations, especially when environments and microbiomes can both change over time?

To date there is considerable evidence that host genetics can contribute to several microbiome phenotypes, including gut microbial community composition, microbial richness, and the relative abundance of certain gut microbes (Blekhman et al., 2015; Busby et al., 2017; Golder, Thomson, Denman, McSweeney, & Lean, 2018; E. Li et al., 2012; Spor, Koren, & Ley, 2011; Turnbaugh et al., 2008). These effects may arise through indirect genetic effects on host behavior and diet, such as lactose tolerance in adulthood, or more directly by host genetic effects on, for example, gut motility, cell-to-cell signaling, the permeability of intestinal epithelial cells, stomach acidity, and insulin secretion (Beasley, Koltz, Lambert, Fierer, & Dunn, 2015; Blekhman et al., 2015; Davenport et al., 2015; Kreznar et al., 2017; Rawls, Mahowald, Goodman, Trent, & Gordon, 2007; Spor et al., 2011; Zhao et al., 2013). However, measuring the heritability of gut microbiome phenotypes is difficult for at least three reasons. First, genetic and environmental effects are frequently confounded (Wagner et al., 2016). Relatives are often close social partners, and as a result, they may share similar environments and consume similar diets; hence, in addition to being colonized by the same environmental microbes, relatives may also exert similar selective regimes in their guts (Song et al., 2013; Tung et al., 2015). Likewise, if heritability is measured by comparing phenotype similarity in parents and offspring, this can be confounded if parents directly transmit

microbes to offspring via vertical transmission (Davenport et al., 2015). Second, the magnitude of environmental effects can swamp host genetic effects. Indeed, a recent study found that the effects of host genetic ancestry were undetectable compared with environmental effects (Rothschild et al., 2018). Third, gut microbiome phenotypes are complex and dynamic, changing with short-term fluctuations in diet (David et al., 2014) and long-term shifts between seasons (Amato et al., 2016; Hicks et al., 2018), and as the host ages (Bennett et al., 2016; Ren et al., 2016; Yatsunenko et al., 2012). As a result, the phenotype in question may change considerably over time within single individuals.

Given the confounds and complexities in detecting heritable microbiome phenotypes, we propose three questions that individual-based primate studies are well-suited to answer. The first question is: which microbiome phenotypes are repeatable within an individual host over time? Prior studies have shown that individual hosts exhibit distinctive, persistent gut microbial communities (Caporaso et al., 2011; Degnan et al., 2012; Turnbaugh et al., 2008). However, many of these studies had durations less than one year, raising the question: how long are these signatures maintained? By looking over longer time periods, even as long as host lifespans, it is possible to test which microbial phenotypes persist through changing social and physical environments. Some primate projects have years of banked fecal samples from known subjects, providing individual-based longitudinal data that are not available in other study systems (Alberts & Altmann, 2012; Guevara, Chen-Kraus, Jacobs, & Baden, 2017; Kappeler & Watts, 2012; Moeller, Foerster, et al., 2016). Establishing the repeatability of a trait (i.e., its consistency within an individual over time) is important because it reflects the upper limit of a trait's heritability; that is, if variation in a phenotype has low repeatability, it will also have low heritability (Boake, 1989; Falconer, 1960; Wolak, Fairbairn, & Paulsen, 2011). Hence, pinpointing repeatable microbial phenotypes may suggest which phenotypes might be most heritable.

Second, can we detect heritable gut microbial phenotypes, controlling for local environmental conditions? Long-term primate studies possess several advantages in both defining heritability and in quantifying environmental traits. To date, most studies attempting to measure host genetic effects on the microbiome have used either twin studies (Gomez et al., 2017; Goodrich et al., 2016; Turnbaugh et al., 2008), comparisons between populations (Morton et al., 2015; Yatsunenko et al., 2012), or selectively bred livestock lines (Zhao et al., 2013). Primate studies that have pedigree data permit a more powerful approach, as phenotypes can be tracked through families and over multiple generations. In addition, sex-biased dispersal in many non-human primates breaks up tight correlations between genetic relatedness and shared environments. In primates with female-biased dispersal, for instance, maternal half-siblings in different social groups can be compared to identify maternal effects. More generally, longitudinal samples from dispersing individuals may provide insight into heritability across changing environments. Finally, longitudinal data on individual hosts with known birth dates can be used to control for host age. This is important because health-related phenotypes in hosts, such as body

weight, blood pressure, and basal metabolic rate, have heritability values that decrease with age because environmental variation swamps genetic effects over time (Ge, Chen, Neale, Sabuncu, & Smoller, 2017). By dividing primate data sets into age classes, we can test if microbiome phenotypes likewise demonstrate an age-related decline in heritability, and if this decline could have potential health consequences.

Third and finally, can we determine if heritable microbial species are shared among closely related primate species? Gut microbiome similarity between hosts often reflects host phylogenetic relationships (Kropáčková et al., 2017; Ley et al., 2008; J. Li et al., 2018; Ochman et al., 2010); hence, related host species may likewise share more heritable microbial species than expected by chance, especially if heritable microbes are beneficial to hosts. Primates provide a particularly interesting system to test ideas about host–microbe coevolution and heritability because of the variety of environments primates thrive in (Smuts, Cheney, Seyfarth, & Wrangham, 1987). Humans in particular face different selection pressures than their wild relatives (e.g., live in more artificially constructed environments, consume different diets, etc.), raising the possibility that, counter to the dominant paradigm, humans might not share more heritable microbial species with closely related primates than they do with their more distant relatives. Understanding which gut microbial phenotypes are heritable in wild primates, and which heritable phenotypes are consistent through fluctuating environments and across primate lineages will shed insight on how host selection affects the gut microbiome.

4.4 | Does the gut microbiome show signs of host aging?

Across primates, and indeed across the tree of life, most physical systems—from immune function, to memory and muscle mass—decline with age (Altmann, Gesquiere, Galbany, Onyango, & Alberts, 2010; Bronikowski et al., 2011; Hayward et al., 2015; Nussey, Froy, Lemaitre, Gaillard, & Austad, 2013). However, whether gut microbiomes also senesce is unknown. Healthy microbiomes can change with age, and longitudinal microbiome data are one of the best ways to learn (a) if aging gut microbiomes exhibit systematic and predictable declines in the services microbiomes provide to hosts, (b) what drives these changes, and (c) whether those declines are reflected in generalizable markers of ecosystem function, such as gut microbiome diversity, composition, resilience, or stability (Biagi, Candela, Fairweather-Tait, Franceschi, & Brigidi, 2012; Heintz & Mair, 2014; Saraswati & Sitaraman, 2014). Answering these questions is important to discover the gut microbiome's role in age-related changes in human and animal health, to develop gut microbial interventions to improve health in old age, and to learn whether age-related changes in the gut microbiome serve as harbingers of developmental milestones, aging, and mortality (see also Section 4.5). Currently, the vast majority of research on gut microbial senescence is on human subjects (Biagi et al., 2010; Costello et al., 2012; Mai & Morris, 2013; V. J. Martin, Leonard, Fiechter, & Fasano, 2016;

Gerber, 2014). However, such research is currently hampered by two barriers that might be overcome by research on non-human primates. The first barrier is the challenge of collecting detailed microbiome time series from a large number of subjects. Time series are essential to understand aging trajectories in individual hosts, learn why some microbiomes age faster than others, measure age-related changes in gut microbial stability and resilience, and test whether gut microbial stability or variation in rates of gut microbial aging predict disease risk or longevity (Costello et al., 2012; Gerber, 2014; Mai & Morris, 2013; V. J. Martin, Leonard, et al., 2016). Nearly all current studies of human gut microbial aging are cross-sectional (Biagi et al., 2010, 2016; Bian et al., 2017; Claesson et al., 2011; Odumaki et al., 2016). Indeed, to our knowledge, the only longitudinal study on gut microbial aging in humans has just two time points from 26 subjects, collected 3 months apart (Claesson et al., 2011).

A second barrier is the confounds created by human lifestyles, diets, and medications, which affect gut microbial composition and change as human health declines with age (Claesson et al., 2012). These confounds make it difficult to disentangle intrinsic (e.g., immunosenescence, changing gut motility, and mucosal barrier function) from extrinsic (e.g. host environments and behaviors) drivers of gut microbial senescence (Saraswati & Sitaraman, 2014). Moreover, these confounds may explain why patterns of gut microbial senescence in humans are often population specific (Biagi et al., 2010, 2013; Bian et al., 2017; Claesson et al., 2011; Mariat et al., 2009; Odumaki et al., 2016). For example, some studies report rising *Bacteroidetes* during senescence (Claesson et al., 2011; Mariat et al., 2009), while others report the opposite pattern or no trend (Biagi et al., 2010; Bian et al., 2017). Similarly, while the prevailing view is that gut microbial diversity declines in old age (Biagi et al., 2013; Voreades, Kozil, & Weir, 2014), several recent studies find that diversity either does not change or increases in the elderly compared with younger adults (Biagi et al., 2016; Bian et al., 2017; Jackson et al., 2016; Kong et al., 2016; Odumaki et al., 2016). This heterogeneity in age-related changes in diversity is especially important because gut microbial diversity is often proposed to be a marker of microbiome functional stability and host health (see Section 4.5; Costello et al., 2012). In support, low gut microbial diversity is frequently linked to high frailty scores in old age (Claesson et al., 2011, 2012; Jackson et al., 2016; van Tongeren, Slaets, Harmsen, & Welling, 2005). However, the causal pathways connecting host lifestyles, health, frailty, and gut microbial diversity remain completely unknown.

Wild non-human primates may be relatively free from age-related lifestyle confounds. Specifically, wild primates may not exhibit strong changes in behavior or environments as they age; unlike some elderly humans, aging primates do not live in residential care facilities or hospitals. This relative freedom from age-related changes in lifestyle, and primates' evolutionary and ecological similarity to humans, makes them a useful model to illuminate intrinsic patterns and processes of gut microbial senescence. However, the full potential of this approach has yet to be realized. Most research on age-related differences in primate gut microbiomes compares adults to juveniles

(Aivelo, Laakkonen, & Jernvall, 2016; Amato et al., 2014; Springer et al., 2017; Su et al., 2016). More rare are studies that model age as a continuous variable within adults (Degnan et al., 2012; Mitchell et al., 2017; Ren et al., 2016), and only two studies have directly compared gut microbial differences in prime age and senescent adults (Bennett et al., 2016; Trosvik et al., 2018). The picture emerging from these studies is intriguing: unlike in humans, studies on non-human primates have yet to find a relationship between old age and gut microbial diversity; instead, diversity is similar in senescent versus prime age adults (Bennett et al., 2016; Mitchell et al., 2017; Ren et al., 2016; Trosvik et al., 2018). In terms of gut microbial composition, baboons (*P. cynocephalus*), vervets (*Chlorocebus aethiops sabaeus*), and geladas (*Theropithecus gelada*) all exhibit few or no effects of age on the identity and abundance of gut microbial taxa (Mitchell et al., 2017; Ren et al., 2016; Trosvik et al., 2018). Age-related compositional changes are more pronounced in ring-tailed lemurs (*Lemur catta*), but the effects of social group and habitat quality are much stronger (Bennett et al., 2016). Interestingly, one study of captive vervet monkeys (*C. aethiops sabaeus*) found that old monkeys did not differ in gut microbial composition from younger adults, despite exhibiting several other physical differences that should affect the gut microbiome, including systemic inflammation, poor intestinal barrier function, and reduced intestinal motility (Mitchell et al., 2017).

Together, these studies provide just a glimpse into primate gut microbial senescence, but their results strongly implicate extrinsic factors unique to humans (e.g., health care, medication, assisted living), and not intrinsic factors fundamental to primate senescence in human gut microbial aging. Moreover, they suggest that studies linking gut microbial diversity to frailty in humans might arise from an indirect path (poor health leads to residential care and medications, which, in turn, reduce gut microbial diversity) as opposed to a direct causal path between gut microbiome diversity and host health. However, much more research is needed to resolve these causal connections. Researchers studying non-human primates are well positioned to disentangle comparative processes underlying signatures of aging in gut microbiomes. Key questions include: what features of gut microbial senescence, if any, are universal across primates? And what are the underlying processes that generate age-related changes in diversity, stability, and composition? Understanding these processes and resulting patterns is essential to design effective gut microbiome interventions to promote healthy aging, and which signatures of gut microbial senescence are effective markers of host health.

4.5 | Do gut microbiome composition and dynamics predict host fitness and health?

Individual variation in gut microbiome composition has repeatedly been linked to host health (Claesson et al., 2012; Greenblum, Turnbaugh, & Borenstein, 2012; Kostic et al., 2015; Subramanian et al., 2014), but the features that separate “unhealthy” from “healthy” microbiomes remain largely unknown. Differentiating

healthy from unhealthy microbiomes may be useful for understanding health disparities in humans and animals, but it's also relevant to ecology and evolution for at least two reasons. First, ecologists and evolutionary biologists are often interested in measuring an animal's fitness, and animal “health,” including microbiome health, may serve as a useful proxy for fitness. In other words, “healthy” microbiomes may sometimes also be “fit” microbiomes. Second, community ecologists often use concepts such as stability and resilience to define community or ecosystem health, in part because these traits may predict community diversity and productivity (Lehman & Tilman, 2000; Rapport, Costanza, & McMichael, 1998). Because microbiomes are themselves complex communities, stability and resilience may provide useful measures of microbiome health.

In order to test these ideas, many researchers have called for prospective, longitudinal, population-based studies (Mai & Morris, 2013; R. Martin, Makino, et al., 2016). Such studies would measure microbiome composition and dynamics in a cohort of subjects, ideally at multiple time points, and then follow up with these subjects over time to test whether microbiome markers predict host health or fitness outcomes (Figure 4). Studies like these provide an essential complement to controlled experiments that manipulate microbiome composition in captive animals. This is because what population-based studies lack in experimental control, they make up for in naturalism. Importantly, microbiomes in captive primates differ considerably from their wild relatives (Amato, 2013; Clayton et al., 2016; Hird, 2017). While captive primate microbiomes may be more similar to human microbiomes, it is also challenging to recreate natural environmental, disease, dietary, and social effects in captivity that likely drive microbiome dynamics in the wild.

Non-human primates are ideal for testing the relevance of microbiome dynamics to host health due to the availability of robust longitudinal and demographic data and their evolutionary relatedness to humans. In addition to tracking individual subjects over time, many primatologists collect data on animal health and performance, including the incidence of illness, parasite infection, observational signs of poor health, fertility, maturational milestones, and lifespan (Alberts & Altmann, 2012; Lonsdorf, Travis, Pusey, & Goodall, 2006). Non-human primates also parallel humans in development and lifespan; all primates are long-lived, altricial organisms that have an extended juvenile period and relatively slow life histories. However, compared with humans, non-human primates have much shorter generation times and lifespans, making it more feasible to track individuals from birth to death, and even across generations.

Studies that adopt *prospective longitudinal study designs* to test the relationship between microbiome composition and host health or fitness outcomes are rare. The few studies that have been done focus on health in early life. For example, a small prospective, longitudinal study conducted by Madan et al. (2012) in human infants found that premature infants who maintained high gut microbial diversity did not develop neonatal sepsis during the follow-up period. Additionally, Zhou et al. (2015) found that gut microbial composition in premature infants predicted the onset of necrotizing enterocolitis. To our

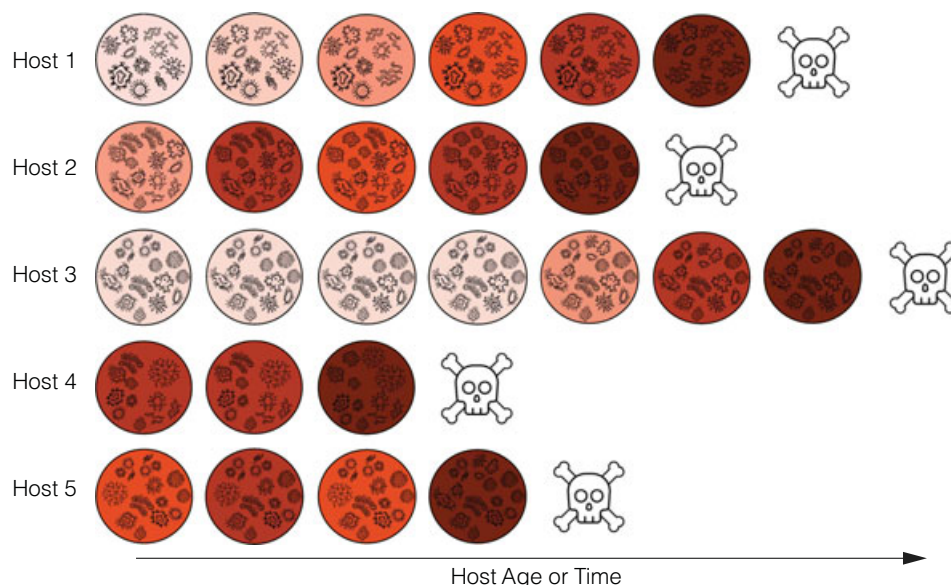


FIGURE 4 Prospective, longitudinal sampling of gut microbial dynamics. Each row represents an individual host, and each circle represents a gut microbiome sample. The color gradient represents changes in microbial composition and/or dynamics that are proposed to be predictive of host death, represented by the skull. Darker colors represent microbiome features that predict death; samples are darkest (least healthy) before the host dies, and the host with the longest lifespan experiences a long period of microbiome health, represented by the series of samples with light colors. Short-lived hosts have samples with consistently dark colors

knowledge, no studies have yet used a prospective, longitudinal design to connect the gut microbiome to fitness components, such as lifespan or reproductive success in a natural non-human primate population. However, experiments in several captive systems suggest there may be links here. In the short-lived killifish (*Nothobranchius furzeri*), for example, transferring the microbiome from captive 6-week-old fish into captive antibiotic-treated 9.5-week-old fish increased killifish lifespan significantly (P. Smith et al., 2017). Similarly, male *Drosophila* inoculated with a commensal species from the genus *Lactobacillus* experienced longer mating periods and higher offspring production (Morimoto, Simpson, & Ponton, 2017). In contrast, *Drosophila* inoculated with a *Acetobacter* species produced daughters with significantly smaller body mass, which may reduce fecundity and other markers of fertility (Morimoto et al., 2017).

Finally, all of the studies reviewed above focus on one-time measures of either gut microbial diversity or composition as markers of healthy microbiomes. No studies in natural systems have yet used longitudinal microbiome data to test the power of gut microbial stability or resilience for predicting host health, fertility, or survival (see Box 2; Sommer, Anderson, Bharti, Raes, & Rosenstiel, 2017). However, experimental studies exploring how the humanized mouse gut microbiome recovers from different types of gastrointestinal infections have found that hosts that fail to return to their original gut community conformation are less healthy than mice that exhibit gut microbial resilience (Buffie et al., 2012; Hsiao et al., 2014; Schwab et al., 2014).

Non-human primates are ideal for connecting the microbiome to host health and fitness, not only because of their evolutionary and physical similarity to humans, but also the broader evolutionary consequences of the microbiome and its role in conservation.

Prospective, population-based longitudinal data from non-human primate systems will be essential to answering questions such as: how does the gut microbiome change with long-term health? Are gut microbial diversity, stability, or resilience useful markers of host health or fitness? If so, why? If not, “multi-omics” approaches may uncover functional pathways or metabolic products that are useful, specific markers of host health. If the gut microbiome can be leveraged as a noninvasive biomarker of host health, such a marker would be especially powerful as it would encompass the quality of the host’s diet and environment both before sample collection and into the future. As such, understanding the role of the gut microbiome in health and fitness could help monitor host diet, habitat, and health noninvasively (Trevelline, Fontaine, Hartup, & Kohl, 2019; West et al., 2019).

5 | CONCLUSIONS AND FUTURE DIRECTIONS

During the last two decades, major advances have been made in understanding the factors shaping the primate gut microbiome (e.g., Amato et al., 2015, 2016; Moeller, Foerster, et al., 2016; Moeller et al., 2013; Tung et al., 2015). However, for primates, and indeed for most other animals, research on the microbiome is largely cross-sectional or limited to only a few time points. As such, we have not yet captured the highly dynamic nature of vertebrate gut microbiomes. Measuring this dynamism and uncovering its underlying ecological processes, will require dense time series data from multiple hosts. In most vertebrates, the expense and time involved in capturing these time series data is prohibitive. In this review, we have made the argument that field-based

primate studies, owing to their focus on the lives of individual animals and the relative ease of collecting longitudinal fecal samples from known animals, are better positioned to collect these data than studies of humans or many other species. However, analyzing the resulting data will be challenging. Capturing time-evolving (i.e., dynamic) features of microbiomes across multiple subjects is both more statistically challenging and computationally intensive than analyzing cross-sectional data. However, new methods are being developed every day, and SSMs may provide a particularly valuable approach (see Section 3 and Box 3).

In the future, we believe that research on microbiome dynamics will benefit from being guided by basic principles of community dynamics, summarized in the four ecological processes of dispersal, selection, drift, and speciation (Vellend, 2016; Vellend & Agrawal, 2010). Interpreting multidimensional time series data is difficult without appropriate principles and theory. Thus, viewing the microbiome through the lens of these overarching processes will facilitate and guide researchers from diverse scientific disciplines in studying primate gut microbiomes. As Koskella et al. (2017) concisely stated: "It is important that we avoid 'reinventing the wheel' by ignoring existing theory, but also do not blindly apply theory without understanding the important nuances of host-associated [microbiomes]" (Koskella et al., 2017, p. 1613). While the field certainly benefits from borrowing principles and theory from ecology, there is an urgent need to develop theory specific to the microbiome that incorporates the many complexities and nuances of the microbiome.

Finally, we suggest five questions that we believe are particularly fruitful avenues where longitudinal primate studies are well positioned to fill key major gaps in microbiome dynamics. While our review largely focuses on 16S rRNA amplicon sequencing, rapid progress may entail longitudinal sampling combined with "multi-omic" approaches, such as transcriptomics, proteomics, and metabolomics. We are not aware of any such longitudinal studies to date, but it is certain that such approaches will allow for a considerably higher resolution and more insight into the dynamic interplay between hosts and microbes, including the functional changes that emerge from it.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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